Remarks

I. Status of Claims.

Claims 1-13 are pending in the application. Claims 1-13 are rejected. Applicant respectfully requests reexamination and reconsideration of the case in light of the following remarks. Each of the rejections levied in the Office Action is addressed individually below.

II. Amendment to claims.

Rejected claims 7 and 8 have been cancelled.

Rejected claims 1, 2, 4, 12, and 13 have been amended.

Claim 4 has been amended to specify that the *size* of the polymeric carrier is larger than the renal excretion limit. Support for this amenmdent can be found in the specification (page 8, lines 15-17; and page 9, lines 6-19).

Claims 1, 2, 12, and 13 have been amended to specify that (a) the recognition segment is an oligopeptide, and (b) that the digestive enzyme is either a serine protease or a matrix metalloproteinase. Support for this amendment can be found in the application as filed (Appendix A) and in original claim 7.

Applicant submits that no new matter has been added to the application by the present amendment.

Applicant specifically reserves the right to pursue the subject matter of the original claims in a related application; the present Amendment is introduced for the *sole* purpose of focusing the issues in this case and speeding its progress toward allowance. Applicant respectfully requests reexamination and reconsideration of the present case, as amended.

III. New claims.

New claims 14-56 have been added.

Claims 14 and 44 has been added to specify that the polymeric carrier in the conjugate is dextran. Support for new claim 14 can be found in the specification (page 10, lines 4-6; page 32,

Example 1; page 38, Example 3; page 39, Example 5; page 44, Example 8; page 56, Example 10; and page 57, Example 12).

Claims 15, 16, 23, 45, 46, and 53 have been added to specify that the oligopeptide recognition segment comprises IPVGLIG. Support for these new claims can be found in the specification (page 35, lines 19-21).

Claims 17-20 and 47-50 have been added to specify that the drug is methotrexate. Support for these new claims can be found in the specification (page 42, Example 7; page 44, Example 8; page 55, Example 9; page 56, Example 10; page 56, Example 11; and page 57, Example 12).

Claims 21-22 and 51-52 have been added to specify that the drug molecule is doxorubicin. Support for these new claims can be found in the specification (page 32, Example 1; page 35, Example 2; page 38, Examples 3 and 4; page 39, Example 5; and page 41, Example 6).

Claims 24-43 have been added to further specify the identity of the digestive enzyme. Support for these new claims can be found in the application as filed (Appendix A).

Claims 54-56 have been added to specify that the conjugate is used to treat certain diseases or disorders. Support for these new claims can be found in the specification (page 31, line 20-page 32, line 3; and page 42, line 21-page 43, line 1).

Applicant submits that no new matter has been added to the application by the present amendment.

IV. Rejection under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claim 4 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner states that the claim language, "the polymeric carrier is larger than the renal excretion limit" is indefinite. The Examiner interpreted the phrase to mean "a concentration of polymer determined through experiment to reach the renal excretion limit." Applicant respectfully submits that this interpretation is at odds with the teachings of the specification. On page 2, lines 7-9, the specification states that "[i]n preferred embodiments the

polymeric carrier is greater in *size* than the renal excretion limit." Therefore, Applicant has amended claim 4 to read, "the *size* of the polymeric carrier is larger than the renal excretion limit" in order to clarify the apparent ambiguity. Applicant respectfully submits that the rejection is rendered moot by the present Amendment.

V. Rejection under 35 U.S.C. § 102(b) in view of Duncan *et al.*, (WO 98/56425).

Claims 1-13 are rejected under 35 U.S.C. § 102(b) as being anticipated by Duncan *et al.* (WO 98/56425). The Examiner states that "Duncan teaches prodrugs and the method to make them, the prodrug can be activated by enzymes (injected before or after in the tissue, thus they are overexpressed in that area), in which the drug...is connected covalently to a linker...in which the other end is connected to a hydrophilic polymer." Therefore, the Examiner concludes that Duncan anticipates or renders obvious the claimed invention in the present application. Applicant respectfully disagrees.

As amended, the claims of the present application recite polymer-linker-drug conjugates that release the drug when the linker is cleaved by digestive enzymes that are (a) serine proteases or matrix metalloproteinases and (b) overexpressed in the extracellular space of the target tissue. Duncan does not teach such a polymer-linker-drug conjugate. Instead, Duncan teaches a first conjugate that is cleaved by the exogenous bacterial enzyme β-lactamase and a second conjugate that is cleaved by cathespin B, a cysteine protease. Applicant, therefore, respectfully requests that the rejection be removed.

VI. Rejection under 35 U.S.C. § 102(b) in view of Saffran *et al.*, (U.S. Patent 4,665,308).

Claims 1-13 are rejected under 35 U.S.C. § 102(b) as being anticipated by Saffran *et al.* (U.S. Patent 4,665,308). The Examiner states that "Saffran teaches a method of producing and using vinyl esters...containing cross-linked azo bonds...for releasing therapeutic agents...into the lower GI tract through reduction by azo reductases." Therefore, the Examiner concludes that Saffran anticipates or renders obvious the claimed invention in the present application. Applicant respectfully disagrees.

Saffran describes a two-component system in which azo-containing polymeric materials encapsulate a therapeutic agent within a polymeric resin. Saffran does not describe a polymeric carrier conjugated to a therapeutic agent; instead, the therapeutic agent is passively trapped within the vinyl ester resin (column 1, lines 66-68; and column 3, lines 32-55). When the azo bonds are degraded by chemical reduction by azo reductases in the GI tract, the resin is dissolved and the therapeutic agent is freed from the resin (column 1, lines 6-68; and column 4, lines 63-68).

As amended, the claims recite a three-component conjugate comprising a therapeutic agent, a polymeric carrier, and a linker that associates the agent to the carrier. Therapeutic agents are released from the conjugate upon cleavage of an oligopeptide recognition segment by serine proteases or matrix metalloproteinases. Saffran does not teach such a three-component conjugate, but instead teaches a two-component system in which azo-containing polymeric materials encapsulate a therapeutic agent within a polymeric resin. Furthermore, Saffran does not teach an oligopeptide recognition segment, but instead teaches a recognition segment comprising an azo bond. Saffran teaches that chemical degradation of the polymeric carrier by azo reductases causes release of the therapeutic agent; in contrast, the present invention teaches that release of the agent is caused by cleavage of the linker moiety by serine proteases and/or matrix metalloproteinases. Saffran does not anticipate the present invention; therefore, Applicant respectfully requests that the rejection be removed.

VII. Double patenting.

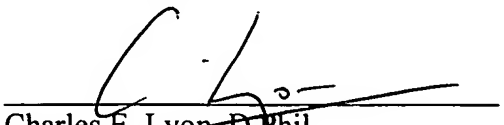
Claims 1-13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 and 16 of co-pending U.S. Patent Application USSN 60/779401. Applicant respectfully defers further comment on this rejection until the claims of either application have been found to be patentable.

VIII. Conclusion.

Based on the arguments presented above, it is submitted that the amended claims are allowable over the art of record. If it is believed that a telephone conversation would help

expedite prosecution of this case, or if any further information is required, the Examiner is invited to contact the undersigned at (617) 248-4793. Additionally, please charge any fees that may be required, or credit any overpayment, to our Deposit Account No. 03-1721.

Respectfully submitted,



Charles E. Lyon, D.Phil.
Agent for Applicant
Registration Number 56,630

Patent Department
Choate, Hall & Stewart
Two International Place
Boston, MA 02110
clyon@choate.com
Phone: (617) 248-4793
Fax: (617) 248-4000

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